LATE-LIFE MENTAL ILLNESS RESEARCH AT THE NATIONAL INSTITUTE OF MENTAL HEALTH: AN ANALYSIS OF FISCAL YEAR 2000 GRANTS, CONTRACTS, AND INTRAMURAL RESEARCH PROGRAM PROJECTS

A REPORT OF THE NATIONAL INSTITUTE OF MENTAL HEALTH AGING RESEARCH CONSORTIUM

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NIMH National Institute of Mental Health

The National Institute of Mental Health (NIMH) Aging Research Consortium was established in 2002. Its mission is to:

- Stimulate research on mental health and mental illness to benefit older adults
- Maintain an infrastructure to better coordinate aging research throughout the Institute
- Provide researchers, advocates, and the public with a linkage to the Institute
- Advance research training for the study of late-life mental disorders

The Aging Research Consortium includes NIMH program staff who oversee research studies focused on late-life issues, a representative of the Institute's Division of Extramural Activities (which oversees review of grant proposals), an NIH intramural scientist in the field of aging and mental illness, and invited guests from other Institutes and agencies. Areas of research span the full spectrum of the Institute's interests, including depression, anxiety, Alzheimer's disease, basic neurobehavioral research, schizophrenia, suicide, impact of caregiving, and sleep disturbance. The consortium is also responsible for coordinating research, encouraging knowledge transfer and clinical application of the findings, and providing research policy leadership.

This report describes NIMH's aging research from FY2000 that was commissioned by former Director Steven Hyman, M.D. A workgroup reviewed the Institute's portfolio of aging-related FY2000 grants, ongoing projects of the Intramural Research Programs (IRP), and contracts. Their purpose was to examine the strengths, gaps, and opportunities within particular aging-related disorders (depression, dementia, etc.) as a function of the approach (e.g., etiology, course and risk factors, clinical trials, services research).

Extramural grants to academic institutions, intramural research to NIMH investigators, and contracts were categorized as follows (each grant was assigned to only one category):

Anxiety and somatoform
Bipolar
Caregivers
Dementia and Alzheimer's disease
Depression
Estrogen
General aging research
General research training
Late-life Parkinson's disease
Normative
Schizophrenia
Sleep
Suicide

Program Analysis

Overall Analysis

In FY2000, NIMH aging research included 248 projects funded at $85,230,361. Most of the research falls in three areas: dementia, general aging research, and depression. This report presents research by subject area.

Dementia and Alzheimer's Disease Research (29% of aging research through NIMH)

Dementia and Alzheimer's disease (AD) constitute the largest proportion of research described in this report.

Neuroscience and genetics: This portfolio includes research on transgenic animal models of AD studying pathophysiology, amyloid precursor and tau protein regulation, and the search for novel genes, viral vectors, and microglial neurotoxicity. Intramural investigators are studying apoptosis, neuropeptides in animal memory, and the role of plasmids in AD.

Training, outcome, and survey studies: These studies include Ph.D. training in legal and ethical issues, studies of dementia with Lewy bodies, surveys of elderly cohorts, and the development of devices to track individuals who wander.

Center grants funded by NIMH: One research center grant follows individuals with AD, focusing on disease heterogeneity, and one services center has a partial emphasis on dementia.

Behavioral and treatment research: Studies in this area focus on the management and pharmacologic treatment of agitation, depression, and psychosis in AD. One contract, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE-AD), is a large-scale multi-site trial investigating staged behavioral treatment of AD with antipsychotic medications. One grant tests the use of anti-inflammatory medications and two test psychosocial treatments.

Biomarkers and Clinical Correlates in AD: Many studies and several intramural projects examine biomarkers or clinical correlates. Apolipoprotein E (APO E) genotype as a predictor for AD is a primary focus. Other investigations include imaging studies (positron emission tomography and evoked potentials), sibling genetic searches, clinical neuropsychology (including test development), and longitudinal studies of people "at risk" for developing dementia.

Overall, the Institute has a significant research portfolio on AD. Strengths include behavioral treatment research, which has a fairly tight focus, as well as biomarker research. Opportunities include studies that assess treatment effectiveness, services, and approaches to dissemination. Predictive and longitudinal follow-up studies or a study to combine clinical therapeutics and biomarker evaluation would be timely. Longitudinal research would be helpful in validating measures, characterizing behavioral syndromes (e.g., depression of AD), and identifying risk factors. Prevention of behavioral symptoms has not kept pace with behavioral research.

General Aging Research (23%)

General aging research includes studies that focus on cognitive science and cognitive

neuroscience in adults (e.g., functional magnetic resonance imaging of prefrontal cortex); molecular and cellular neuroscience in adults (e.g., animal research on estrogen and cognition); genetic methods (e.g., development of software for linkage analyses); and research training programs in areas such as neuroscience, behavioral neuroscience, biological sciences, and mental health services. Most of this research is supported in the Division of Neuroscience and Basic Behavioral Science (DNBBS).

Depression Research (18%)

Neuroscience: Imaging studies are geared toward describing morphometry and cerebral metabolism as they relate to geriatric depression and minor depression, including testing hypotheses related to frontal lobe volume loss and the relationship of gray and white matter changes. Several studies focus on using ligands for serotonin receptors and transporters to identify abnormalities. Other research emphasizes the biochemical aspects of depression, examining the role of estrogen and choline.

Psychopathology and course: These studies fall into four broad areas: cardiac/vascular, suicide, disability, and diagnosis/course. The emphases on medical and psychiatric comorbidity, as well as vascular depression, are relative strengths. Depression and cardiac factors are studied in individuals with coronary artery bypass grafts and congestive heart failure. Several projects investigate interventions to reduce the risk of depression; others focus on cerebrovascular factors and depression. Suicide research is examining environmental and genetic predictors of depression and suicide, and exploring factors that lead older adults not to report ongoing suicidal ideation. Disability and its role in depression are being studied, with an emphasis on developing interventions to reduce both. Several studies examine important dimensions of depression, including “traumatic grief,” “depression without sadness,” and minor depression.

Behavioral and treatment research: These studies fall into five broad areas: treatment response, comorbidity, community care, caregivers, and cost of care. Treatment response grants are looking at positive factors such as exercise and brief sleep deprivation, and covariation in drug or cerebral metabolism. Several intervention research centers focus on targeting treatment to specific cohorts and maintaining treatment response. Comorbidity of depression with Parkinson’s disease, alcoholism, personality disorder, melancholia, and physical illness is being studied with respect to depression treatment response. Community care is studied with home care models and through measures and methods development, including telemedicine. Several grants investigate the costs associated with depression treatment.

Overall, depression is a major component of the Institute’s mission. Strengths include the breadth of the portfolio and the intervention research centers. Opportunities remain to develop longitudinal studies of individuals with comorbid depression and other illnesses, studies of novel biological or animal models of depression, and studies of subjects with psychotic depression, dysthymia, or minor depression.

To build on studies investigating medical and psychiatric comorbidities, others could consider research focusing on the course, treatment, and development of specialized measures of assessment and intervention outcome. Treatment studies tend to look at factors related to

treatment response; more research could be done to simply validate treatments and improve their dissemination into the community. The recent Program Announcements for Developing and Advanced Centers for Services and Interventions Research can provide greater focus, as can recommendations from the NIMH Strategic Plan for Mood Disorders Research (http://www.nimh.nih.gov/strategic/stplan_mooddisorders.cfm).

Normative Research (9%)

This section comprises studies of healthy subjects and basic research on functions relevant to aging.

Molecular and cellular mechanisms: These studies look at choline mechanisms, dopaminergic systems, BDNF (brain-derived neurotrophic factor), and stress neuropeptides. Several study molecular/cellular mechanisms in AD, and two involve changes in plasticity with aging. Human studies target various aspects of drug sensitivity and adverse responses to psychotropic medications.

Cognition and memory: Cognition research addresses mechanisms such as perceptual categorization. Projects are evenly divided between those with an aging focus and those involved with general processes. Several studies focus on general memory processes in adults (genetic enhancements in mice, models of working memory, hippocampal systems), while others target aging-related processes. Again, the latter awards are heterogeneous, emphasizing glucocorticoids, APO E, source memory, and prospective memory.

Social processes: These studies include a longitudinal study of aging and studies of ethnic factors and social contexts (e.g., Hispanic and Asian American).

Half of these studies devote only part of their resources directly to aging, and the research foci are diverse and heterogeneous. One exception is late-life studies of emotion and mood, where there are opportunities for studies that are ultimately targeted toward treatment development. For example, longitudinal studies monitoring the onset of psychiatric symptomatology in healthy adults could help integrate the finding that older adults show relatively positive mood states with the contrasting finding that older persons are at increased risk for depression and physical illness.

Perhaps the greatest gains can come from studies examining how aging affects neuropathology, or what factors increase the risk for mental illness in a “normal” older brain. Cell culture models of mental illness are essentially nonexistent, and there are few animal models of mental illness. Human brain imaging and human postmortem brain studies have shown increasing potential as ligands and methods become more sensitive, selective, and sophisticated, and this is a solid area for new studies. Because of significant overlap in this area of emphasis, researchers should coordinate with other Institutes.

Schizophrenia (7%)

Neuroscience: This area includes two centers: one follows individuals with schizophrenia longitudinally and includes brain banking; the other focuses on imaging and correlates. Other

studies focus on cognitive aspects, examining the roles of beta-amyloid, NMDA glutamate receptor hypofunction, and dopamine neuropathologic correlates.

Psychopathology and course: Several imaging studies examine the role of brain laterality in cognitive function. Others include a longitudinal study of late-onset schizophrenia and use of pupillography to measure whether cognitive decline is an aspect of schizophrenia.

Behavioral and treatment research: The center, studies, and training grants focus on two broad themes: the development of tardive dyskinesia and interventions focused on improving cognition and function.

Strengths include three centers, where gains have been made in validating treatment and characterizing symptomatology. This focus comes from NIMH-funded research that started more than a decade ago. Areas where the portfolio might be strengthened include epidemiological and services research. Better outcome measures could be developed, particularly for cognition, as future treatment is likely to be focused in this area. The current emphasis on age-related changes in cognition could expand to test nonbiological models for decrements, and the emphasis on tardive dyskinesia could shift toward long-term use of atypical antipsychotics or factors that lead to enhanced function in the community. Opportunities also exist to validate combination treatments, treatment algorithms, and approaches to rehabilitation and adherence.

General Research Training (3%)

These grants consist primarily of general training grants to institutions that have one or more late-life research faculties. Their research emphases include schizophrenia, psychoneuroimmunology, gender differences, and general psychiatric research training. Fewer than 20 percent of these training efforts relate to aging research. The modest number of entries in this category illustrates an opportunity for more training programs.

Sleep Research (2%)

Research in this area includes basic and clinical studies of bright light therapy to treat sleep disturbances of aging and tests of various pharmacologic and behavioral sleep treatments. Other studies test the effects of exercise or cognitive behavioral therapy on sleep quality.

Caregiver Research (2%)

Most of these studies focus on the relationship between the stress of caring for individuals with AD and behavioral or immunologic markers among caregivers. Longitudinal studies follow caregivers of individuals who have schizophrenia, age-related vision loss, and coronary artery disease. A training grant focuses on the techniques of behavioral studies. Overall, caregiver research would benefit from development, translation, and implementation into services settings (e.g., primary care) and identification of the markers that predict successful function in caregivers.

Suicide Research (2%)

Studies in this area include a large-scale collaborative research project (PROSPECT) designed to identify individuals over the age of 60 at risk for attempting suicide and to provide treatment. Subjects are seen in primary care settings in three metropolitan areas. Other studies identify factors that predict suicide in late-life.

PROSPECT, developed through a Request for Applications, is a model program for NIMH prevention efforts. There is also important basic research on late-life suicide, but it is studied primarily at a single academic institution. Overall, this area appears to be well organized and likely to make significant gains despite its limited size. Inclusion of information on suicide ideation in other ongoing clinical research would help expand the knowledge base significantly.

Late-Life Parkinson's Disease Research (<1%)

Several studies relate to Parkinson's disease (PD) in the elderly.[1] These studies are heterogeneous and tend to focus on basic science.

Anxiety and Somatoform Disorders Research (<1%)

There are three studies in this area: one on generalized anxiety disorder, another under the broad spectrum of "anxiety disorders," and a career award characterizing the course of late-life panic disorder. Overall, the characterization of anxiety in the elderly could be improved, as it differs from anxiety in earlier adulthood and may place a greater burden on general medical care.

Estrogen Research (<1%)

Two of the four studies in this area are interventions—one examining the effects of estrogen on psychopathology and cognition in schizophrenia, and the other in depression. The other studies focus on estrogen and neurogenesis in the hippocampus.

Bipolar Disorder Research (<1%)

Two studies focus on bipolar illness in the elderly: a comparison of the clinical and neuroanatomical features of young and old adults with bipolar disorder and an evaluation of the pharmacokinetics and therapeutic efficacy of mood stabilizers in geriatric mania.

Overall Recommendations

Better coordinate intra-Institute and inter-Institute activities. NIMH's aging research is spread throughout all but two of its research branches (and these are focused on child research), with approximately 30 project officers. The rationale for assigning grants based on methodology is sound; however, a group dedicated to looking across the Institute, such as the Aging Research Consortium, can increase the communication among programmatic areas. In addition, more effort could be directed toward better integration of common agendas among the other Institutes

[1] The Institute also has an official listing of grants considered related to PD. Although PD affects older adults, not all of the Institute's PD research has direct implications for older adults. Note that most of the research listed as PD-related is not coded as age-related under the official coding system.

that share interest in late-life research.

Increase the submission of meritorious late-life research proposals. NIMH funded 248 projects relevant to late-life in FY2000. More high-quality and meritorious proposals must be submitted for late-life research to make significant gains. The Institute, through a consortium, could invigorate late-life research through the use of workshops, program announcements, participation at national meetings, and other initiatives.

Develop state-of-the-art training for late-life researchers. As our nation's population continues to age, there will be an increased need for investigators to tackle late-life research problems. However, few systematic efforts are currently devoted to training the next generation of late-life researchers. The research community could be encouraged to develop innovative training programs beginning at the predoctoral level and extending throughout a research career. This effort would complement the late-life research programs already in place.